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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/475,704	12/30/1999	SUSAN W. BARNETT	1631.002	6738

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EXAMINER	
PITRAK, JENNIFER S	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/475,704	BARNETT ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,10,24-40,42,43,49-60,63-66 and 68-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,24-40,42,43,49-60,63-66 and 68-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Remarks

The finality of the last Office Action, mailed 04/25/2008 is withdrawn in view of further considerations as described herein.

Claims 1-8, 11-23, 41, 44-48, 61, 62, and 67 are canceled. Claims 9, 24, 27, 42, 43, and 49 are amended. Claims 9, 10, 24-40, 42, 43, 49-60, 63-66, and 68-75 are pending and are under examination.

Priority

The instant claims, drawn to expression cassettes comprising SEQ ID NO: 3 and SEQ ID NO: 4 and methods of using these cassettes, have support in the provisional application, 60/152,195 filed 09/01/1999 (Figures 1 and 2). The claims do not have support in the provisional application, 60/114,495 filed 12/31/1998. Applicant's acknowledged that the instant SEQ ID NO: 3 and SEQ ID NO: 4 have support only in the 60/152,195 application in their response filed 12/19/2002. The instant claims are afforded the priority date of 09/01/1999.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9, 10, 24-29, 33, 39, 40, 42-52, 54-60, 63-66, and 68-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Shiver, *et al.*** (WO98/34640, international publication date 08/13/1998; of record 06/12/2000 IDS), **Haas, *et al.*** (1996, Current Biology, v.6:315-24, on IDS dated 10/29/2000), **Persson, *et al.*** (1998, Biologicals, v.26:255-65), and **Novitsky, *et al.*** (1998, direct submission to GenBank, 12/03/1998, Accessions AF110965 and AF110967).

The claims are to expression cassettes comprising polynucleotide sequence, SEQ ID NO: 3 (claim 68) and SEQ ID NO: 4, (claim 69), and to the cassettes further comprising an HIV *pol* gene wherein the *pol* gene has deletions of reverse transcriptase and integrase (claims 9, 10, 68, 69, 72, and 73). SEQ ID NO: 3 is a synthetic *gag* sequence of HIV strain AF110965 and SEQ ID NO: 4 is a synthetic *gag* sequence of HIV strain AF110967, each of which was derived by manipulating codon usage patterns to conform to codons found in highly expressed human genes and to inactivate instability elements (INS). Claims 70 and 71 are to the expression cassette of claims 68 and 69 further comprising an HIV *protease* gene. Claims 42, 43, and 74 are to compositions comprising the expression cassettes of claim 68 or 69 further comprising a *Gag* polypeptide or an adjuvant. Claims 49-52, 54-60, 63-66, and 75 are to methods of generating an immune response in a subject comprising introducing the cassette of claim 68 or 69 by intramuscular injection (claim 75) or by administering the composition of claim 74 into the subject using a gene delivery vector, a particulate carrier, such as a gold or tungsten particle, or by administering the composition encapsulated in a liposome preparation, or by administering the composition of claim 74 and an HIV polypeptide that is administered before, during, or after administration of the composition. Claims 24-26 are to a recombinant expression system comprising the expression cassette of claim 68 or 69, wherein the SEQ ID NO: 3 or SEQ ID NO:

4 is operably linked to an HIV-Ltr or metallothionein promoter. Claims 27-29, and 36-40 are to a cell comprising the expression cassette of claim 68 or 69 wherein SEQ ID NO: 3 or SEQ ID NO: 4 is operably linked to control elements compatible with expression in the selected cell, and wherein the cell is an immortalized or tumor-derived cell, VERO, RD, 293, or a lymphoid cell.

Shiver, *et al.* describe and claim a synthetic polynucleotide comprising a DNA sequence encoding an HIV *Gag* protein wherein the DNA sequence comprises codons optimized for expression in a mammalian host (claim 4). At page 28, Shiver, *et al.* delineate the methods used to generate the synthetic *gag* sequence. These methods include comparing wild type codons to preferred human codons and replacing those non-preferred codons with preferred human codons (steps 2 and 3), and inspecting new gene sequence for undesired sequences generated by the codon replacements, such as ATTTA (AUUUA) sequences, and substituting codons that eliminate these undesired sequences (step 5). At page 15, Shiver, *et al.* teach that their methods can be used to modify any HIV sequences known or later discovered (lines 15-32).

Claim 5 of Shiver, *et al.* is to the polynucleotide having the optimized HIV sequence, wherein the sequence is an HIV *gag*-protease. On page 34, Shiver, *et al.* describe the use of HIV DNA encoding the *gag* and *pol* genes (lines 23-25). Shiver, *et al.* teach that immunization with such an HIV DNA may be achieved by intramuscular injection and that the injection may antedate, coincide, or follow injection with a pharmaceutical composition comprising inactivated HIV-derived proteins (*Gag*) (page 34 and claim 7). Claim 8 of Shiver, *et al.* is to a method for inducing immune responses comprising administration of a synthetic polynucleotide comprising an optimized *gag* sequence and further comprising an adjuvant. Shiver, *et al.* teach plasmid vectors for use in their invention, which can be maintained in prokaryotic cells and from which

the modified HIV gene sequences can be expressed in a subject (p.14, lines 3-37). One embodiment is described as containing a CMV-intA promoter and a transcriptional terminator at the end of the HIV gene coding sequence (p.13, last paragraph). Shiver, *et al.* further teach *in vitro* expression of the HIV gene coding sequences in human RD or 293 cells, which are tumor-derived and immortalized cells, respectively (p.30, example 5). Shiver, *et al.* teach that gold microparticles or liposome preparations can be used to deliver the vectors (p.5 first paragraph and page 23, lines 6-37). The expression vectors of Shiver, *et al.* express T-helper cell and CTL epitopes because they elicit CTL, humoral and helper T cell responses (p.34, lines 4-18; claim 10).

Shiver, *et al.* do not explicitly teach the use of lentiviral vectors. Shiver, *et al.* do not explicitly teach an expression cassette comprising both the modified *gag* sequences and a sequence encoding an HIV polymerase polypeptide in which the reverse transcriptase (RT) and integrase (*int*) coding regions have been deleted, wherein the modified *gag* sequences were derived from wild-type HIV strains AF110965 and AF110967.

Haas, *et al.* teach improved HIV gp120 gene expression in human cells by modifying the gp120 codon usage to conform to that of highly-expressed human genes (abstract; p.315 third paragraph – p.316). The authors indicate that HIV-1 envelope proteins are natural targets for vaccines and for post-infection treatments, but that the expression of such genes is limited (p.315, third paragraph). Haas, *et al.* point out that their study was an attempt to address the low-expression problem by considering the profound codon usage bias of the *env* proteins and the authors further indicate that such bias extends to the *gag* and *pol* proteins (p.315, third paragraph). Haas, *et al.* constructed a synthetic gp120 gene based on a known HIV strain

wherein the wild-type HIV codons were changed to better match the codons of highly expressed human genes shown in Figure 1, which have higher GC-content than do HIV codons (p.316). The synthetic gp120 gene was more efficiently expressed in 293T cells compared to the unmodified gp120 gene (Figure 3, p.317 and text p.316, "Expression of wild-type and synthetic gp120"). At page 319, Haas, et al. discuss the phenomenological rules for the inefficiently-expressed codon patterns found in HIV, which includes 1) preferred codons maximize the number of adenine residues in the viral RNA, 2) T is preferred over C whenever the third position degeneracy is a pyrimidine, and 3) the dinucleotide CG is highly under-represented.

Novitsky, *et al.* teach the wild-type *gag* sequences of HIV-1 type C strains AF110965 and AF110967.

Persson, *et al.* teach HIV-1 retrovirus-like particles for expressing HIV proteins for use as a vaccine. These particles have a large deletion in the HIV-1 *pol* gene, which eliminated RT and *int* (abstract; p.256, second paragraph; p.257, Figure 1). Persson, *et al.* also teach that these virus-like vectors may better elicit an immune response than subunit vaccines because the vectors more accurately present native viral epitopes by producing particles with native conformations (p.255, second column).

It would have been obvious to one skilled in the art at the time of the instant application to alter the *gag* sequence of the HIV-1 Type C strains AF110965 and AF110967, taught by Novitsky, *et al.* by altering the codon-usage of the sequence and by removing the INS elements, as taught by Shiver, *et al.* and Haas, *et al.* Shiver, *et al.* and Haas, *et al.* demonstrated that such techniques improved HIV-1 gene expression and Shiver, *et al.* showed that such techniques improved immune responses against HIV. Shiver, *et al.* further indicated that their methods of

gene sequence alteration could be applied to any HIV *gag* sequence to improve the expression of the gene in host cells. One of ordinary skill in the art would have immediately recognized the benefit of such alterations to the HIV-1 gene sequences because the same alterations had proven to increase expression of those genes. One of skill in the art would have been fully capable of applying this known technique to any HIV-1 *gag* sequence for the purpose of improving expression of the gene in human cells and the results would have been predictable. It further would have been obvious to use a viral vector in which the RT and *int* regions were deleted, because Persson, *et al.* teaches that such vectors are safer than those without these regions deleted and that virus-like particles may better represent the native epitopes than subunit vaccine vectors. Thus, it would have been obvious to modify the *gag* sequences of HIV strains AF110965 and AF110967 according to the guidelines of Shiver, *et al.* and further to construct the vectors, cells, and methods of using the vectors according to the teachings of Shiver, *et al.* and Persson, *et al.* Therefore, the instant claims would have been obvious to one skilled in the art at the time of the instant application.

Claims 9, 10, 24-29, 33, 39, 40, 42-60, 63-66, and 68-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Shiver, *et al.*, Haas, *et al.*, Novitsky, *et al.***, and **Persson, *et al.***, as applied to claims 9, 10, 24-29, 33, 39, 40, 42-52, 54-60, 63-66, and 68-75 above, and further in view of **March, *et al.*** (1998, U.S. Patent 5,797,870).

Claims 9, 10, 24-29, 33, 39, 40, 42-52, 54-60, 63-66, and 68-75 are described above. Claim 53 is to a method of generating an immune response in a subject comprising introducing a

composition comprising the expression cassette of claim 68 or 69, wherein the expression cassette is introduced using a Sindbis-virus derived vector.

Claims 9, 10, 24-29, 33, 39, 40, 42-52, 54-60, 63-66, and 68-75 are obvious over Shiver, *et al.*, Haas, *et al.,* Novitsky, et al, and Persson, *et al.* as set forth in the above rejection under 35 U.S.C. 103(a). These references do not teach the use of a Sindbis-virus-derived vector for introduction of the expression cassette.

March, *et al.* teach methods of gene therapy, which requires delivery of gene expression vectors (abstract). At column 5, lines 15-19, March, *et al.* teach that the vectors can be Sindbis virus vectors among other viral vectors.

It would have been obvious to one skilled in the art at the time of the instant application to use a Sindbis-virus-derived vector for expression of modified *gag* sequence cassettes. Shiver, *et al.*, Haas, *et al.,* Novitsky, *et al.*, and Persson, *et al.* collectively teach expression of modified *gag* sequences from plasmid and lentiviral (HIV) vectors. March, *et al.* teach that several viral vectors can be used for gene expression in a subject, including Sindbis virus vectors. Thus, one of skill would immediately recognize that a Sindbis virus vector could easily be substituted for a lentiviral vector for expression of the modified *gag* sequence cassette in a subject with a clear expectation of success and predictable results. Thus the claims would have been obvious at the time of the instant application.

Claims 9, 10, 24-40, 42-52, 54-60, 63-66, and 68-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Shiver, *et al.*, Haas, *et al.,* Novitsky, *et al.*, and Persson, *et al.***, as

applied to claims 9, 10, 24-29, 33, 39, 40, 42-52, 54-60, 63-66, and 68-75 above, and further in view of **Kapitonov, *et al.*** (2001, U.S. Patent 6,280,989, filed 06/17/1999).

Claims 9, 10, 24-29, 33, 39, 40, 42-52, 54-60, 63-66, and 68-75 are described above. Claims 30-32 and 34-38 are to a cell comprising the expression cassette of claim 68 or 69 operably linked to control elements, wherein the cell is a CHO, Sf9, Tn5, yeast, plant, B-cell, T-cell, or primary cell.

Claims 9, 10, 24-29, 33, 39, 40, 42-52, 54-60, 63-66, and 68-75 are obvious over Shiver, *et al.*, Haas, *et al.,* Novitsky, et al, and Persson, *et al.* as set forth in the above rejection under 35 U.S.C. 103(a). These references do not teach the expression cassette(s) in all of the instantly claimed cells, including 293, CHO, Sf9, Tn5, yeast, plant, B-cell, T-cell, and primary cells.

Kapitonov, *et al.* teach host cells for expression vector expression including 293, CHO, Sf9, Tn5, yeast, plant, B-cell, T-cell, or primary cells (column 15, lines 30-40).

It would have been obvious to one skilled in the art at the time of the instant application to use 293, CHO, Sf9, Tn5, yeast, plant, B-cell, T-cell, or primary cells as host cells for the claimed expression cassettes. Shiver, *et al.*, Haas, *et al.,* Novitsky, *et al.*, and Persson, *et al.* collectively teach expression of modified *gag* sequences from plasmid and lentiviral (HIV) vectors. Kapitonov, *et al.* teach that many cell types are useful for expressing genes from expression vectors and that these cells include 293, CHO, Sf9, Tn5, yeast, plant, B-cell, T-cell, or primary cells. Thus, one of skill would immediately recognize that any of these cells could easily be substituted for the RD and 293 cells taught by Shiver, *et al.* with a clear expectation of success and predictable results. Thus the claims would have been obvious at the time of the instant application.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak, PhD
Examiner
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